Annals of Clinical and Analytical Medicine
Original Research

Postoperative pelvic irradiation and vaginal brachytherapy in stage II endometrial cancer

Pelvic radiotherapy and vaginal brachytherapy in stage II endometrial cancer

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Abstract

Aim: Stage 2 endometrial cancer is a heterogeneous disease and has a low incidence. The aim of this study is to examine the oncological results in patients with stage 2 endometrial cancer who received pelvic radiotherapy and vaginal brachytherapy (VBT).

Material and Methods: Between 2000-2020, all operated eighty patients with stage 2 endometrial cancer were included in the study. Patients were analyzed in terms of baseline characteristics, adjuvant radiation (RT) planning modality, intracavitary VBT, chemotherapy (CT), local relapse, distant failure, overall survival (OS), and disease-free survival (DFS).

Results: At the end of a median follow-up of 82 months, none of the patients who underwent pelvic external RT and VBT had vaginal/pelvic failure. It was observed that there was a 13-fold increase in the risk of mortality in patients aged 60 years and older (HR=13,2 ; 95% CI=1.89–92.07, p=0.09). The 5- and 10-year OS rates were 92% and 86%, 5 and 10-year DFS rates were 94% and 91%, respectively.

Discussion: In the presence of poor prognostic factors in stage 2 endometrial cancer, pelvic external RT and VBT is an effective adjuvant treatment methods with excellent oncological results.

Keywords

Stage II Endometrial Cancer, Radiotherapy, Brachytherapy

DOI: 10.4328/ACAM.21529 Received: 2022-12-01 Accepted: 2023-01-13 Published Online: 2023-02-03 Printed: 2023-05-01 Ann Clin Anal Med 2023;14(5):388-393
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This study was approved by the Ethics Committee of Istanbul Prof. Dr. Cemil Tascioglu City Hospital (Date: 2022-10-17, No: E-48670771-514.99)

Introduction

Endometrial cancer is one of the most common cancers in women worldwide. At the time of diagnosis, endometrial cancer that confined to the uterus is seen in approximately 67%, which is associated with higher survival rates [1]. The most important prognostic factors are old age, stage, grade, depth of myometrial invasion, lymph node involvement, tumor size, lymphovascular space invasion (LVSI) and poor histology [2, 3] . The surgical staging system, developed in 1988 by the International Federation of Gynecology and Obstetrics was updated in 2009. Formerly both endocervical glandular invasion and stromal invasion were included in stage II. With the revision in 2009, the definition of Stage 2 disease was defined as the presence of only cervical stromal involvement (both microscopically and macroscopically) without extending beyond the uterus and lymph node involvement [4].

Among all endometrial cancers, stage 2 disease is thought to be approximately 5-8% [5,6]. Cervical stromal involvement is important as it is associated with an increased risk of LVSI and lymphatic metastases [7,8].

According to some recurrence prediction models, cervical stromal invasion was also observed to be among the risk factors [9]. Although its incidence is low in all stages, it is a very heterogeneous group in terms of histological grade, depth of myometrial invasion, LVSI status, extent of cervical invasion, molecular subtype, presence of serous/ clear cells [10]. Which of these subgroups has an indication for external pelvic RT, in whom vaginal brachytherapy (VBT) alone is sufficient, who should receive systemic treatment, or how chemotherapy (CT) and RT should be combined, etc., questions await answers.

Our knowledge of stage 2 disease to date is generally based on subgroup analyzes of large-scale clinical trials [3, 11, 12]. In this study, our goal is to report the treatment approaches and results of the patients with cervical stromal invasion limited to the uterus, which has a narrow area among all endometrial cancer patients. In addition, another aim is to examine in detail postoperative external pelvic RT and brachytherapy applications in this group of patients in terms of dose, technique and disease control.

Material and Methods

Study Population

Between 2000-2020, patients who applied to our center with the diagnosis of endometrial cancer were evaluated retrospectively. According to the guidelines of the International Federation of Gynecology and Obstetrics (FIGO 2009), postsurgical eighty patients with stage 2 were included in the study [4]. All patients were analyzed in terms of age at diagnosis, comorbidity, type of surgery, histology, grade, tumor size, depth of myometrial invasion, stage, LVSI, type of lymphadenectomy, number of dissected pelvic/paraaortic lymph nodes, adjuvant radiation (RT) planning modality, intracavitary VBT, chemotherapy (CT), local relapse, distant failure, overall survival, and progression-free survival. The study protocol was approved by the Ethics Committee of Istanbul Prof. Dr. Cemil Tascioglu City Hospital.

Postoperative Pelvic External Beam Radiation Therapy (EBRT)

Before 2008, RT planning was applied to patients as a 2-dimensional (2-D) anterior-posterior pelvic region. In the 2008-2012 period patients were treated as 3D conformal box technique with a belly board in order to reduce the intestinal dose. Since 2012, the volumetric modulated arc therapy technique (VMAT) has been used for patients.

Simulation

All patients underwent computed tomography simulation with a Philips Brilliance (Amsterdam, Switzerland) scanner. In order to better protect the surrounding tissues at risk such as the rectum, bladder and bowel, both before the simulation and before each treatment, the patients were made to drink 1-1.5 liters of water to adjust the bladder fullness, and bowels were emptied using anti-constipation medication. The patients were immobilized in the supine position and the pelvic region between L1 and the upper 1/2 of the femur was imaged with axial 3mm sections. These computed tomography simulation images were transferred to the Varian Eclipse TPS station (Varian Medical Systems, Palo Alto, CA) for target volume delineation.

Volume Definition

Clinical target volumes (CTV) were delineated according to the Radiation Therapy Oncology Group (RTOG) contouring guidelines. The entire vaginal stump, paravaginal-parametrial tissues, common iliac (up to L4-L5 interspace)- external-internal iliac nodal regions, presacral lymph node regions were included in the treatment area with a safety margin of 7-15 mm. Also, bladder, rectum, bowel and femoral heads were delineated as the organs at risk (OAR).

Radiotherapy Planning

Plans were designed with volumetric arc technique (dual-spring) according to healthy tissue tolerance dose limits. Treatment was delivered on a Rapidarc – Trilogy linear accelerator using two arcs that rotate 360° in opposite directions (179° clockwise and 181° counterclockwise). The collimator angle was set to 30°/330°. Planning was done with Eclipse version 10.0 using 6MV high energy photon energy. The suitability of the radiotherapy plans was checked by examining the isodose curves and dose-volume histograms (DVH). The daily treatment time was approximately 5 to 8 minutes. Weekly cone-beam computed tomography (CBCT) and daily kilovoltage (KV) imaging were taken to monitor the RT field in the patients.

Brachytherapy

Brachytherapy was performed as 2-D before 2013, and the dose was defined to point A. As of 2013, 3-D brachytherapy applications have been started. The treatments were administered in 3-5 fractions, usually every other day, with a cylinder applicator suitable for the patient's vagina anatomy. Before each treatment, the patients were given a diet program and treatment preparation was made by bowel cleansing with enemas at night and in the morning. HDR Nucletron device with iridium 192 source was used for the treatment. Before the cylinder application, the bladder was emptied by inserting a Foley catheter. After the application, the patient was immobilized in accordance with the treatment position and computed tomography simulation images were obtained. These images were transferred to the Nucletron Oncentra Brachy treatment planning system for intracavitary brachytherapy planning.

Target volumes were delineated in accordance with the recommendation of the American Brachytherapy Society (ABS).

The treatment doses were defined to the upper 1/3 vaginal surface and the full length of the vagina for serous and clear cell histologies. Bladder, rectum, sigmoid, urethra, and small intestine were delineated as the organs at risk (OAR). OAR dose tolerance limits were taken into consideration according to ABS guideline recommendations (Figure 1).

Statistical Analysis

The descriptive statistics of the numerical variables obtained in the study are given as the median (range) value. The descriptive statistics of the categorical variables are given as numerical values and percentages. Data distribution was assessed by the Kolmogorov–Smirnov test. In consideration of the sample size, the non-normal distribution of variables was assumed, and nonparametric tests were used for between-group comparisons. Thus, categorical and numerical variables were compared using the chi-square test and the Mann–Whitney U-test, respectively. Endpoint definitions: local failure (time to any locoregional event related to EC), distant progression (time to any non-regional event related to EC), OS (time to any death), and disease-free survival (time to any event related to EC). The follow-up time for the patients were measured from the date of surgery. Kaplan–Meier curves were generated for overall survival (OS) and disease-free survival (DFS) and significance was assessed using the log-rank test. Frequency tables and statistics were performed using SPSS 25 software (SPSS Inc., Chicago, IL, USA). The probability value of $p<0.05$ was considered significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

Patient Characteristics

The median age of the patients was 57,5 (range, 35-86). Median follow-up was 82 (range, 9-273) months. 54% of the patients had an additional comorbid disease. 83,8 % of the cases had endometrioid tip adenocancer (IDC) histology. The baseline characteristics of the patients are presented in Table 1. All patients underwent TAH+BSO. The median tumor size was 4,5 cm (range: 1-13). Lymphadenectomy was applied to 66% of the patients. 21 % of the patients received adjuvant chemotherapy and the regimen was carboplatin paclitaxel. Considering the statistical analysis, it was observed that the depth of myometrial invasion and LVSI were higher in patients aged 60 years and older (p=0.006, p=0.001, respectively). Also, an increase in the incidence of positive LVSI, deep myometrial invasion and high grade histology was observed in patients with a tumor size of 2 cm or more (p=0.034, p=0.041, p=0.008 respectively) (Table 2).

Adjuvant Radiotherapy Details

All patients underwent postoperative pelvic external RT and VBT. The median dose of RT administered was 46 Gy (45-50 Gy) and the median dose of VBT was 18 Gy (15-28,5 Gy). The prescribed pelvic RT doses were 50,4 Gy/28fr (27 % pts), 50 Gy/25fr (20% pts), 48 Gy/24fr (2% pts), 46 Gy/23fr (25% pts), 45 Gy/25fr (26% pts). The prescribed VBT doses were 27,5 Gy/5fr (12,5 % pts) , 25 Gy/5fr (7,5 % pts), 24Gy/3fr (11% pts), 20 Gy/4fr (6 % pts), 18 Gy/3fr (33 % pts), 15 Gy/3fr (30 % pts). Treatment Details are presented in Table 3.

Oncological Results

After a median follow-up of 82 months, no local recurrence was observed in any patient. Only one patient died due to disease. Ten patients died due to non-disease reasons. Distant metastasis was encountered in five of the patients. The sites of metastasis were the peritoneum, paraaortic area, abdominal lymphatic,

Table 1. Patient and tumor characteristics

	Patients (n:80,%)
Age	Median; 57,5 (range 35-86)
<60 years	48 (60%)
≥60 years	32 (40%)
Comorbidity	
Hypertension	30(37,5%)
Coronary heart disease	6 (7,5%)
Diabetes mellitus	14 (17,5%)
Dyslipidemia	4 (5%)
Other	10 (12,5%)
BMI (kg/m^2)	31,25 (23,24-36,33)
Histology	
Endometrioid	67 (83,8%)
Adenosquamous	3 (3,8 %)
Serous	6 (7,5 %)
Clear cell	2 (2,5%)
Myometrial invasion	
<1/2	33 (41,3 %)
≥1/2	47 (58,8 %)
LVSI	
Yes	39 (48,8 %)
No	41 (51,3 %)
Tumor Size	
≤2 cm	8 (10%)
2–4 cm	17 (21,3%)
≥4 cm	55 (68,8%)
Tumor grade	
G1	22 (27,5%)
G2	40 (50 %)
G3	18 (22,5%)

LVSI: Lymphovascular space invasion

Table 2. Comparison of grade, LVSI and myometrial invasion with age and tumor size

	Age			Tumor Size		
	<60 years	≥60 years	P value	<2 cm	≥ 2 cm	P value
Grade						
I	15 (31,9%)	8 (24,2%)	0.704	6 (75%)	17 (23,6%)	0.008
II	22 (46,8%)	16 (48,5%)		2 (25%)	36 (50%)	
III	10 (21,3%)	9 (27,3%)		0 (0%)	19 (26,4%)	
LVSI						
Yes	15 (31,9%)	24 (72,7%)	0.001	1 (12,5%)	38(52,8%)	0,034
No	32 (68,1%)	9 (27,3%)		7 (87,5%)	34 (47,2%)	
Myometrial invasion						
<1/2	27 (57,4%)	8 (24,2%)	0.006	6 (75 %)	27(37,5%)	0.041
≥1/2	20 (42,6%)	25 (75,8%)		2 (25%)	45 (62,5%)	

LVSI: Lymphovascular space invasion

Table 3. Treatment details

	Patients (n: 80, %)
Lymphadenectomy	
Only pelvic	30 (37,5 %)
Pelvic + paraaortic/ Paraaortic sampling	23 (28,75 %)
None	27 (33,75 %)
Number of LNs removed	
Number of pelvic LNs removed	Median; 14 (range 1-69)
Number of paraaortic LNs removed	Median; 11 (range 1-36)
Chemotherapy	
No	63 (78.8 %)
Yes	17 (21.3 %)
RT Planning Modality	
2-D	9 (11%)
3-D	16 (20%)
VMAT	55 (69 %)
Brachytherapy	
2-D	29 (36%)
3-D	51 (64%)

2-D: 2-dimensional, 3-D: 3-dimensional, VMAT: volumetric modulated arc therapy technique

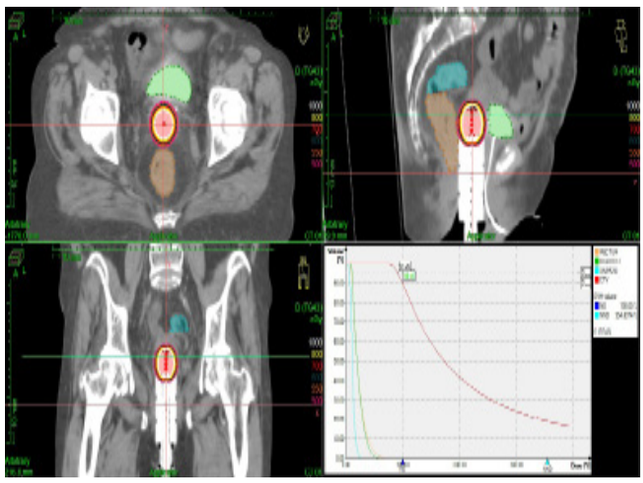

Figure 1. An example of vaginal brachytherapy planning. The isodose distribution with cylinder application in axial, coronal and sagittal views and the dose-volume histogram (DVH).

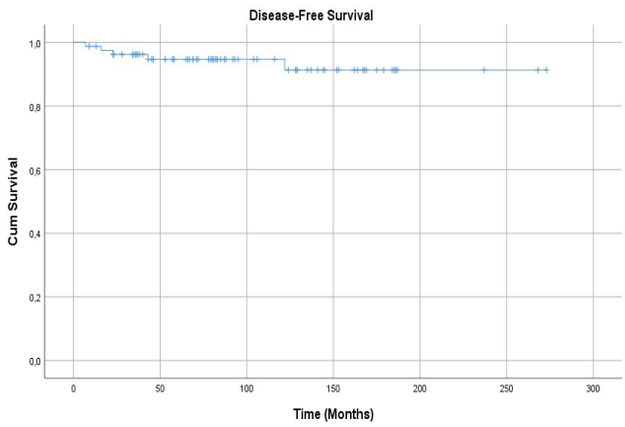

Figure 2. Kaplan-Meier plots of disease free survival

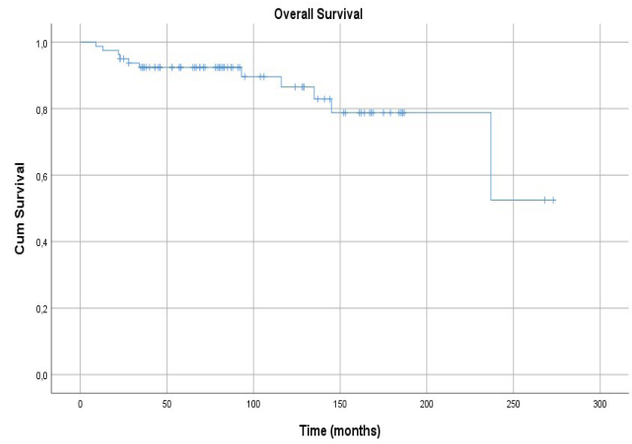

Figure 3. Kaplan-Meier plots of overall survival

median time to metastasis were 23 months (7-122 months). As salvage treatment, one patient received metastasectomy followed by CT, and the other patients received CT. There was no difference in local control, distant metastasis, or overall survival between patients who received and did not receive CT. While the rate of metastasis was 3% in patients with dissected pelvic lymph nodes 10 or more, it was 8.5% in patients with less than 10, but this difference did not reach statistical significance. When the factors affecting survival were examined, it was observed that only age was significant in both univariate and multivariate analyzes. It was observed that there was a 13-fold increase in the risk of mortality in patients aged 60 and over (HR=13,2; 95% CI=1.89–92.07, p=0.09). The 5 and 10 year OS rates were 92% and 86%, the 5 and 10 year DFS rates were 94% and 91%, respectively (Figure 2-3).

Discussion

When the patients in the present study were evaluated in terms of prognostic factors, 10% of the patients had unfavorable histology, 40% of the patients were 60 years and older, 58.8% of the patients had deep myometrial invasion, and 48.8% were LVSI positive. The rate of patients who did not undergo any pelvic sampling was 33.75%. With these features, it was observed that none of the patients who received pelvic external RT and VBT had vaginal/pelvic failure.

Vetter et al. analyzed 9.690 patients with stage 2 endometrial cancer using the national cancer database. When the treatment modalities were examined, EBRT alone, VBT alone and EBRT+ VBT were applied to 16.1%, 27.5%, and 24.4% of the patients, respectively. CT was applied to 14.3% of the patients. When the oncological results were examined, a decrease in the risk of death was observed in patients who received RT alone and RT combined with chemotherapy. When compared to the RT alone group, they found that the risk of death was lower in the RT combined with CT group [5].

Harkenrider et al. retrospectively analyzed the data of 106 patients who received VBT alone for stage 2 endometrial cancer in a multicenter study. Only patients with endometrioid type histology were included in the study. 88.6% of patients were grade 1 or 2, 98.1% had microscopic cervical stromal invasion, 89.6% had pelvic lymph node dissection. With the

median 39-month follow-up, the five-year rate of pelvic recurrence, distant metastasis, and DFS were 4.2, % 7.2% and 74%, respectively. In conclusion, it was emphasized that only VBT could be an option only in a selected group of patients with low risk [13].

Lee et al. examined patients with stage 2 according to FIGO 2009 in their national cancer database and reviewed the results of 2261 postsurgery patients with endometrioid-type histology. Advanced age, African-American race, inadequate lymph node sampling, and high histological grade were found to be independent poor prognostic factors for stage 2 disease. When they compared the patient groups with EBRT, EBRT + VBT and VBT alone, no difference was observed between the three modalities in patients who did not undergo lymphatic dissection. But they observed that the overall survival results were better in the VBT alone group in patients who underwent lymphatic dissection. These results were explained by the fact that the VBT alone group consisted of patients with lower grade, higher lymph node sampling rate and negative LVSI [14].

Chen et al. reported a median 64.6-month single-center results of 110 patients from 1990 to 2013. According to their analysis, 70.9 % of the patients received EBRT+VBT, 13.6% received EBRT alone and 13.6% received VBT alone. CT was applied to 19.1% of the patients. In the study, locoregional recurrence was observed in 5 patients . The time to recurrence was observed as 17.5 months. Distant metastasis was observed in 17 patients, and 14 of these patients were in the EBRT +/- VBT group. The absence of pelvic lymph node dissection and the use of VBT alone, although on the border of statistical significance, were observed as predictive factors for locoregional recurrence. In the survival analysis, the 5-year overall survival rate in patients with grade 3 or poor histology was 65.8% for the EBRT ± VBT group and 33.3% for the VBT alone group (p = 0.020) [6].

Paulson et al. obtained stage 2 endometrial cancer patient's surveillance and reporting records from the cancer registry data. Two hundred sixty four patients who had received adjuvant RT were examined in terms of oncological outcomes according to whether they received mini-pelvic field + VBT , full-pelvic field RT + VBT and VBT alone. It was stated that recurrence-free survival did not differ between these three groups. In addition, when all subgroups were examined, it was observed that CT increased recurrence-free survival and that the mini-pelvic field + VBT group provided disease control similar to the fullc group. In conclusion, they emphasized that mini-pelvic field + VBT can be applied in patients with negative LVSI and no lymph node involvement, full-pelvic field RT +/- VBT can be applied in patients who have not undergone pelvic lymphatic dissection, and VBT alone can be applied in low-risk stage II patients [15].

In the ESGO/ESTRO/ESP guidelines, EBRT is recommended for stage 2 endometrial cancer, and it is reported that only VBT can be considered for stage 2 grade 1, LVSI negative patients [16].

In the NCCN guidelines, EBRT and/or VBT is recommended for the adjuvant treatment of Stage 2 disease. There is a category 2B level recommendation for CT. In addition, it is emphasized that only VBT may be an option in patients with grade I-II myometrial invasion depth below 50%, LVSI negative and cervical stromal invasion at microscopic level.

Conclusion

Stage 2 endometrial cancer is a highly heterogeneous group. Larger series and prospective randomized studies are needed in terms of which RT modality will be appropriate in which subgroup. When treatment planning, prognostic factors should be considered and current guidelines should be followed. However, DFS and OS results are excellent with appropriate treatment selection on a patient basis.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:
Necla Gurdal, Ozge Kandemir Gursel, Binnur Donmez Yilmaz, Nihal Dizdar, Bekir Eren, Mehmet Yalciner, Yakup Büyükpolat, Tanju Berber, Selvi Dincer, Halil Akboru, Hilal Irem Acan, Cakir Numanoglu, Yaren Ceran, Gizem Nur Can, Nurgul Yasar, Berna Akkus Yildirim. *Postoperative pelvic irradiation and vaginal brachytherapy in stage ii endometrial cancer. Ann Clin Anal Med 2023;14(5):388-393*

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